IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Ashkenazi et al.	Docket No:	39780-1618P2C32
Serial No:	09/902,903	Group Art Unit:	1647
Filed:	July 10, 2001	Examiner:	Bunner, Bridget E.

For: **SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME**

AMENDMENT AND RESPONSE TO FINAL OFFICE ACTION

BOX AF
Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

In response to the Office Action mailed on May 19, 2003 in connection with the above-identified patent application, please enter the following amendments, and consider the following arguments. This response is timely filed concurrently with the filing of a Notice of Appeal and is accompanied by a Petition for an Extension of time for two months and necessary fees.

CERTIFICATE OF MAILING (37 CFR 1.10(a))

CERTIFICATE OF MAILING BY "EXPRESS MAIL" - Rule 10: I hereby certify that this correspondence is being deposited on October 20, 2003 with the U.S. Postal Service "Express Mail Post Office to Addressee" under 37 CFR 1.10 as **Express Mail No. EV346725534US** addressed to: Mail Stop: AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Date: October 20, 2003

Cheryl Ann Rogers

In the Claims:

1-38. (Previously canceled).

39. (Previously amended) An antibody that specifically binds to the polypeptide shown in Figure 86 (SEQ ID NO:245).

40. (Previously added) The antibody of Claim 39 which is a monoclonal antibody.

41. (Previously added) The antibody of Claim 39 which is a humanized antibody.

42. (Previously added) The antibody of Claim 39 which is an antibody fragment.

43. (Previously added) The antibody of Claim 39 which is labeled.

44. Previously canceled.

Remarks/Arguments

The foregoing amendments in the specification and claims are of formal nature, and do not add new matter.

Claims 39-43 are pending in this application and are rejected on various grounds. Claim 44 was previously canceled without prejudice or disclaimer. Although the Examiner withdrew some objections and rejections, all claims remain rejected under 35 USC §101, for alleged lack of utility and 35 USC §112, first paragraph for alleged lack of teaching on how to use the claimed invention.

Rejections to the present claims are respectfully traversed.

Claim Rejections – 35 USC § 101/112

Claims 39-43 were rejected under 35 USC §101 as allegedly not being supported by either a credible, specific and substantial asserted utility, or a well established utility. Further, Claims 39-43 were rejected under 35 USC § 112, first paragraph, as allegedly not teaching one skilled in the art how to use the claimed invention.

The Examiner alleges that the teaching in the specification is vague. The Examiner asserts that in the absence of teaching of concentration studies of PRO293 in the assay, PRO293 allegedly could have been utilized at toxic levels in the assay which killed the PDB12 pancreatic ductal cells; the Examiner also alleges that the inhibition results could be due to natural dying off of cells. Thus, the Examiner questions whether PRO293 specifically inhibits protein production. Further, the Examiner alleges that there was lack of disclosure in the specification for disorders involving protein secretion by the pancreas. Thus the Examiner concludes that "the proposed uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the antibodies that specifically bind PRO293 polypeptides."

Applicants respectfully disagree with all the above allegations.

Applicants once again submit that the teaching in Example 70 of the specification is detailed and sufficient for one skilled in the art to determine effective concentrations for

PRO293. The level of skill of cell biologists is very high and they would have no problems to determine effective concentrations of PRO293 that inhibit PDB12 proliferation, using this assay from the present disclosure.

To address the Examiner's concerns regarding "toxic concentrations of PRO293" and specificity of the PDB12 assay, Applicants have enclosed a Declaration by Dr. Jean-Phillipe Stephan, an expert in the PDB12 cell inhibition assay, who has extensively used this assay to test various polypeptides. As Dr. Stephan explains,

> ".... I have personally conducted experiments in which I tested the effect of various other proteins like monoclonal antibodies and HIS-6 tag fusion proteins on PDB12 cell proliferation. In this assay, I tested the effect of up to 100 μg/ml of proteins and did not observe any non specific effect of various proteins on the PDB12 cell proliferation. These data were published in Stephan et al., *Endocrinology* 140:5841-5854 (1999) and Stephan et al., *J. Dev. Biol.* 212:264-277 (1999) enclosed herein (Exhibits B and C), and demonstrate that the PDB12 cells respond specifically to proteins/polypeptides up to a concentration of 100 μg/ml. Therefore, it is my considered scientific opinion that the observed results are not due to non-specific damage of the PDB12 cells".

This shows that the PDB12 cells can tolerate and respond well to fairly high concentrations (upto 100 μg/ml) without dying or getting damaged. Further, Dr. Stephan also says:

> "...I would like to point out that polypeptides like PRO211, PRO287, PRO301 and PRO293 that tested positive in the PDB12 assay were part of a large library of proteins/polypeptides, all or most of which were tested in the PDB12 cell proliferation assay. Therefore, those proteins that did not show any effect on the PDB12 cells could be considered as negative internal controls and additionally demonstrate the specificity of the effects of polypeptides like PRO211, PRO287, PRO301 and PRO293 in the PDB12 assay."

Thus, this shows that the results of the PDB12 assay is specific for the polypeptide being studied. Regarding the Examiner's allegation regarding the "lack of disclosure in the specification for disorders involving protein secretion by the pancreas", Applicants submit that the specification clearly states on page 207, lines 3-4 that "PRO polypeptides have efficiency in inhibiting protein production by PDB12 pancreatic ductal cells and are therefore, useful in

therapeutic treatment of disorders which involve protein secretion by the pancreas, including diabetes, and the like". Further, in his declaration Dr. Stephan explains that ,

> "The PDB12 cell line, also known as "BUD," (Stephan et al., *J. Dev. Biol.* 212:264-277 (1999); Stephan et al., *Endocrinology* 140:5841-5854 (1999) – Exhibits B and C) is an embryonic pancreatic ductal epithelial cell line established from rat pancreatic bud epithelium isolated from 12 days rat embryo. This cell line had been initially established in order to study pancreatic differentiation. Since PDB12 cells have been considered to potentially represent the pancreatic ductal progenitor cells, compounds that test positive in a PDB12 cell proliferation/ inhibition assay are considered to potentially affect pancreatic ductal (and possibly islet) cell progenitor functions *in vivo*. In addition, compounds that have an inhibitory effect in this assay could potentially be used in the treatment of pancreatitis, or pancreatic cancer (e.g. pancreatic ductal cell carcinoma) that benefit from the inhibition of ductal cell proliferation".

Regarding treatment or diagnosis of disease using anti-PRO293 antibodies, as indicated above, Applicants have asserted a specific and substantial use for PRO293 polypeptides in treating pancreatic disorders, like diabetes (emphasis added), and no further research is required by the skilled artisan for determining this asserted utility. Applicants further submit that since the level of skill in the art is high, one skilled in the art would know that based on the disclosure, the agonistic PRO293 antibodies would be useful for treating pancreatic disorders. This logic underlying the asserted utility in the present case would be considered credible by a person of ordinary skill in the art and as set forth in M.P.E.P, 2107 II (B) (1) a rejection based on "lack of utility" should not be imposed. It is, of course, always possible that an invention fails on its way of development to a commercial product. Despite recent advances in rational drug design, a large percentage of drug candidates fails, and never makes it into a drug product. However, the USPTO is not the FDA, the law does not require that a product (drug or diagnostic) be currently available to the public in order to satisfy the utility requirement. Also, the experimentation required to determine the optimal quantity, duration and method of administration is routine in the art is not considered undue experimentation.

Since Applicants have asserted a specific and substantial use for PRO293 and have also taught how to use the present invention, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-1618P2C32). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: October 20, 2003

Daphne Reddy

Daphne Reddy
Reg. No. 53, 507

HELLER EHRMAN WHITE & McAULIFFE LLP
Customer No. 35489
275 Middlefield Road
Menlo Park, California 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Ashkenazi et al.	Group Art Unit 1647
App. No.	:	CERTIFICATE OF EXPRESS MAILING
Filed	:	I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to Commissioner of Patents, Washington D.C. 20231 on:
For	: SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME	(Date)
Examiner	:	

Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF JEAN-PHILLIPE STEPHAN, Ph.D UNDER 37 C.F.R. § 1.132

I, Jean-Phillipe Stephan, Ph.D. declare and say as follows: -

1. I am a Scientist in the Assay and Automation Technology department at Genentech, Inc., South San Francisco, CA 94080, the assignee of the above-identified patent application.
2. I am familiar with the PDB12 cell inhibition assay described in the above-identified patent application, and have personally conducted or supervised experiments for testing various compounds using this assay.
3. My scientific Curriculum Vitae, including my list of publications, is attached to and forms part of this Declaration (Exhibit A).
4. The PDB12 cell proliferation assay has been widely used to study cell viability and proliferation. Easy to implement, this assay incorporates a fluorometric/colorometric growth indicator based on the detection of metabolic

activity. Specifically, the system incorporates an oxidation-reduction (REDOX) indicator that both fluoresces and changes color in response to chemical reduction of growth medium resulting from cell growth. Indeed, the internal environment of a proliferating cell is more reduced than the one of a non-proliferating cell, and the ratios of NADPH/NADP, FADH/FAD, FMNH/FMN, and NADH/NAD increase during cell proliferation. Such metabolic intermediates can reduce the AlamarBlue™ and trigger fluorescence/color changes which could be monitored at 570 nm and 600 nm. Using AlamarBlue™ fluorescence as read-out, the PDB12 cell inhibition assay allows the analysis of the PDB12 rat pancreatic ductal cell proliferation/viability in response to various molecules, for example, the PRO293 polypeptide. The PDB12 cell line, also known as "BUD," (Stephan et al., *J. Dev. Biol.* 212:264-277 (1999); Stephan et al., *Endocrinology* 140:5841-5854 (1999) – Exhibits B and C) is an embryonic pancreatic ductal epithelial cell line established from rat pancreatic bud epithelium isolated from 12 days rat embryo. This cell line had been initially established in order to study pancreatic differentiation. Since PDB12 cells have been considered to potentially represent the pancreatic ductal progenitor cells, compounds that test positive in a PDB12 cell proliferation/inhibition assay are considered to potentially affect pancreatic ductal (and possibly islet) cell progenitor functions *in vivo*. In addition, compounds that have an inhibitory effect in this assay could potentially be used in the treatment of pancreatitis, or pancreatic cancer (e.g. pancreatic ductal cell carcinoma) that benefit from the inhibition of ductal cell proliferation.

5. I understand that according to the Patent Office, the results of the PDB12 assay could be construed by one skilled in the art as natural dying off of pancreatic ductal cells with no effect of the polypeptide on protein production by the cell. To eliminate this possibility, I have personally conducted experiments in which I tested the effect of various other proteins like monoclonal antibodies and HIS-6 tag fusion proteins on PDB12 cell proliferation. In this assay, I tested the effect of up to 100 µg/ml of proteins and did not observe any non specific effect of various proteins on the PDB12 cell proliferation. These data were published in Stephan et al., *Endocrinology* 140:5841-5854 (1999) and Stephan et al., *J. Dev.*

Biol. 212:264-277 (1999) enclosed herein (Exhibits B and C), and demonstrate that the PDB12 cells respond specifically to proteins/polypeptides up to a concentration of 100 µg/ml. Therefore, it is my considered scientific opinion that the observed results are not due to non-specific damage of the PDB12 cells.

6. Regarding controls, I would like to point out that polypeptides like PRO211, PRO287, PRO301 and PRO293 that tested positive in the PDB12 assay were part of a large library of proteins/polypeptides, all or most of which were tested in the PDB12 cell proliferation assay. Therefore, those proteins that did not show any effect on the PDB12 cells could be considered as negative internal controls and additionally demonstrate the specificity of the effects of polypeptides like PRO211, PRO287, PRO301 and PRO293 in the PDB12 assay.
7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

By: _____ Date: 10/15/2003
Jean-Phillipe Stephan, Ph.D.

CURRICULUM VITAE

First name: **Jean-Philippe**
Middle name: **François**
Last name: **STEPHAN**

birth date: 12/01/67
citizenship: French
US immigration status: permanent resident
married, two children

ADRESSES

Home:

Apt. 320 c Lansdale Avenue,
MILLBRAE, CA 94030, USA
Phone/fax: 650-652-9822

Professional:

GENENTECH Inc.,
1 DNA Way,
SOUTH SAN FRANCISCO, CA 94080-4990, USA
Phone: 650-225-3912
Fax: 650-225-1770
Email: stephanj@gene.com

CURRENT POSITION

Since November 1998 – Currently Research Scientist at Genentech, Inc. (Assay and Automation Technology Department).
In this department I am responsible for the development of cell-based assays and technologies in order to support the Oncology and medicinal chemistry projects

EDUCATION

1997 - 1998 **Postdoctoral fellow at Genentech, Inc.**
Theme: Selective cloning of cell surface proteins involved during pancreatic development.
Director: Dr. Jennie P. Mather, Genentech, Inc., 1 DNA way, South San Francisco, USA

1993 – 1996 **Thèse d'Université de Biologie (Ph.D.),** with highest distinction, University of Paris VI
Theme: Implication of cytokines and peptides in the paracrine regulation of spermatogenesis.
Director: Dr. Bernard Jégou, GERM-INSERM U435, Université de Rennes I, Rennes, France

1991 - 1992 **Diplôme d'Etudes Approfondies de Physiologie de la Reproduction/Biologie cellulaire (Diploma in Specialized Studies)**, with distinction, University of Paris VI
Theme: In vitro study of interleukin-1α and 6 in rat Sertoli cells.
Director: Dr. Bernard Jégou

1987 - 1991 **Maîtrise de Biologie Cellulaire (Master in Cellular Biology)**, with distinction, University of Rennes I.

FELLOWSHIPS AND AWARDS

Ph.D. Student Fellowship, December 1993 – December 1996, Ministry of Health and Sciences, France.

Young Promising Scientist Award, *9th European Testis Workshop on Molecular and Cellular Endocrinology*. April 14-19 1996, Geilo, Norway.

Serve as reviewer for the Nucleic Acids Research (NAR)

LANGUAGES

English: fluent
French: native speaker

PUBLICATIONS

PAPERS

STEPHAN J.P., GUILLEMOIS C., JEGOU B. and BAUCHE F. Nitric oxide production by Sertoli cells in response to cytokines and lipopolysaccharide. (1995) *Biochemical and Biophysical Research Communications*, 213, 218-224.

SYED V., **STEPHAN J.P.**, GERARD N., LEGRAND A., PARVINEN M., BARDIN C.W., JEGOU B. Residual bodies activate Sertoli cell IL-1α release, which triggers IL-6 production by an autocrine mechanism, through the lipoxygenase pathway. (1995) *Endocrinology*, 136, 7, 3070-3078.

JEGOU B., CUDICINI C., GOMEZ E. and **STEPHAN J.P.** Interleukin-1, Interleukin-6 and the Germ Cell-Sertoli Cell Cross-talk. (1995) *Reproduction, Fertility and Development*, 7, 723-30.

PIQUET-PELLORCE C., GOMEZ E., CUDICINI C., **STEPHAN J.P.**, DEJUCQ N. and JEGOU B. Cytokines and spermatogenesis. In: Fertility and Sterility: a current review. Proceedings of the XVth World Congress on Fertility and Sterility (Hedon B., Bringer J. & Mares P., Eds). Parthenon publishing group, London, UK. 249-255.

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STEPHAN J.P., CHAO S. Gene expression analysis using RNA/DNA extracted from formalin fixed – paraffin embedded minute tissue samples. *In preparation.*

STEPHAN J.P., MARKER P., CUNHA G. and MATHER J.P. Implication of EpCAM during prostate development and tumor. *In preparation.*

PATENTS

WPI Acc No: 2000-452179/200039
Immunizing a host mammal to produce population of monoclonal antibodies that bind to antigens of specific cell type comprises introducing viable cells with serum-free surfaces.
Inventor: BALD L N; MATHER J P; ROBERTS P R; **STEPHAN J F**
Patent: WO 200037503 A1 20000629 (WO 99US30741)

WIPO/Univentio. All rts. reserv. 00860723
Secreted and transmembrane polypeptides and nucleic acids encoding the same polypeptides/ secretes et transmembranaires et acides nucleiques.codant lesdits polypeptides.
Inventor: BAKER K., DESNOYERS L., GERRITSEN M., GODDARD A., GODOWSKI P. J., GRIMALDI J. C., GURNEY A. L., SMITH V., **STEPHAN J-P.**, WATANABE C., WOOD W.,
Patent: WO 200193983 A1 20011213 (WO 0193983)

Composition and methods for the diagnosis and treatment of disorders involving angiogenesis.
Inventors: BAKER K., FERRARA N., GERBER H., GERRITSEN M., GODDARD A., GODDOWSKI P., GURNEY A., HILLAN K., MARSTERS S., PAN J., **STEPHAN J.P.**, WATANABE C., WILLIAMS P.M., WOOD W., YE W.
U.S. Patent Application.

Methods and composition for detection and quantification of nucleic acid analytes.
Inventors: BILLECI T., JHURANI P., **STEPHAN J.P.**, TSAI S.P., VASSER M., WATANABE C., WONG W.L.
U.S. Patent Application.

Cell and tissue arrays and microarrays and methods of use.
Inventors: FRANTZ G., PEAL F., PHAM T., **STEPHAN J.P.**
U.S. Patent Application.

2 other patent applications submitted (As 05/01/02).

COMMUNICATIONS :

SYED V., **STEPHAN J.P.**, GERARD N., LEGRAND A., PARVINEN M., BARDIN C.W., JEGOU B. Residual bodies activate Sertoli cell interleukin-1 (IL-1) release, which triggers interleukin-6 (IL-6) production by an autocrine mechanism, through the lipoxygenase pathway. *XIIth North American Testis Workshop*, "Function of Somatic Cells in the Testis". April 13-16 1993, Tampa, Florida, USA.

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STEPHAN J.P., SYED V., JEGOU B. Intra- and extracellular Sertoli cell IL-1 and IL-6. *8th European Workshop on Molecular and Cellular Endocrinology of the Testis*. March 27-31 1994, De Panne, Belgium.

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BAUCHE F., **STEPHAN J.P.**, JEGOU B. Induction of a macrophage-like nitric oxide synthase in cultured rat Sertoli and peritubular cells. *9th European Testis Workshop on Molecular and Cellular Endocrinology*. April 14-19 1996, Geilo, Norway. Award for young researcher.

STEPHAN J.P., BALD L., ROBERTS P. and MATHER J.P. Characterization of various antibodies raised to antigens from pancreatic cell lines. *Genentech Inc. Offsite conference*. April 6-9 1997, Asilomar, California, USA.

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STEPHAN J.P., ROBERTS P., BALD L., LEE J., GU Q., HELMRICH A., BARNES D., DEVAUX B. and MATHER J.P. Distribution and function of the rat homologue of the adhesion molecule BEN during development. *38th congres of the American Society of Cell Biology*. December 12-16 1998, San Francisco, California, USA.

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STEPHAN J.P., CHAO S., TSAI S.P. Gene expression analysis using RNA/DNA extracted from minute formalin-fixed, paraffin-embedded tissue samples. 14th Annual the San Diego conference: Nucleic acid technologies in disease detection. November 17th, 1999, San Diego, California, USA.

TSAI S.P., BILLECI T.M., JHURANI P., VASSER M., **STEPHAN J.P.** Improvement of nucleic acid capture-based technologies via 3'-(alpha) ethylene glycol scaffolding. Genentech Pharmacological Sciences Offsite 2000. November 6-9th, 2000. Clear Lake, California, USA.

STEPHAN J.P., BILLECI T.M., DEVAUX B. Anti-tumor antibody generation and characterization by integrated whole-cell immunization and immunoarray analysis. Genentech Pharmacological Sciences Offsite 2000. November 6-9th, 2000. Clear Lake, California, USA.

TSAI S.P., MAUSISA G., TUCKER A.L., WILLIAM P.M., MALLOY B., SMITH J., SOLAR G., EATON D., WONG W.L., **STEPHAN J.P.** Quantification of human hemoglobin genes in SPDI screening. Genentech Pharmacological Sciences Offsite 2000. November 6-9th, 2000. Clear Lake, California, USA.

TSAI S.P., TOMLINSON E., MOFFAT B., TRAN D., STEWART T., **STEPHAN J.P.** FGF19 transgenic mice are hyperphagic and lean: The assay side of this metabolic story. Genentech Pharmacological Sciences Offsite 2000. November 6-9th, 2000. Clear Lake, California, USA.

STEPHAN J.P., MAO W., Rabkin R., FILVAROFF E., PAN J.P. Non TGF-β mediated induction of collagen IV accumulation by human renal proximal tubular cells in response to albumin. Genentech Pharmacological Sciences Offsite 2000. November 6-9th, 2000. Clear Lake, California, USA.

BATAILLE A., TSAI S.P., ZHANG-KLOMPUS Y., WONG W.L., **STEPHAN J.P.** Serum DNA for pharmacogenomic studies HER2 and P53 gene analysis in the context of Herceptin clinical trial as preliminary study. Genentech Pharmacological Sciences Offsite 2000. November 6-9th, 2000. Clear Lake, California, USA.

DAO L.N., **STEPHAN J.P.**, CHAO S., STEFANICH E., FUNELAS C., PANGILINAN P., WOODS C., MORTENSEN D., SUN Y.N., FIELDER P.J. Temporal and dose relationships between plasma GH levels and expression of GH-dependent genes in rats. Genentech Pharmacological Sciences Offsite 2000. November 6-9th, 2000. Clear Lake, California, USA.

QUAN Z., FINKLE D., ASGHARI V., KLOSS J., KOEPPEN H., HALL L., YANG N., **STEPHAN J.P.**, WONG W.L., SLIWKOWSKI M.X., ERICKSON S.L. Pretreatment of MMTV-human Her2 transgenic mice with mu4D5 significantly reduces mammary tumor incidence. Molecular targets and cancer therapeutics: Discovery, Biology, and Clinical applications. AACR-NCI-EORTC International Conference. October 29 – November 2, 2001. Miami Beach, Florida, USA.

FRENCH D., NICHOLES K., WRIGHT B., FRANTZ G., PHAM T., DILLARD-TELM L., TSAI S.P., **STEPHAN J.P.** and STEWART T. A mouse model of hepatocellular carcinoma: ectopic expression of FGF19 in skeletal muscle of transgenic mice. National Meeting – American College of Veterinary Pathologists, December 8, 2002.

ORAL COMMUNICATIONS :

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